DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 2003N–0502]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Study to Measure the Compliance of Prescribers With the Contraindication of the Use of Triptans in Migraine Headache Patients With Vascular Disease

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

DATES: Fax written comments on the collection of information by [*insert date 30 days after date of publication in the* **Federal Register**].

ADDRESSES: OMB is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202–395–6974.

FOR FURTHER INFORMATION CONTACT: Karen L. Nelson, Office of Management Programs (HFA–250), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–1482.

SUPPLEMENTARY INFORMATION: In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Study to Measure the Compliance of Prescribers With the Contraindication of the Use of Triptans in Migraine Headache Patients With Vascular Disease

Migraine headache affects about 20 million Americans. Over the last decade, numerous drugs in a category referred to as ‘‘triptans’’ have been shown to be efficacious in treating migraine headache and have been approved for this condition. Triptan drugs have been prescribed to millions of patients. However, triptans are routinely contraindicated in patients with vascular diseases due to associated rare occurrence of myocardial infarction, stroke, and other ischemic events. In view of the wide use of this class of drugs and the potential impact on public health as a result of this contraindication, FDA believes it would be significantly helpful to better understand the prescribing practices for these drugs.

FDA plans to examine the feasibility of using the Internet to recruit triptan-user migraine headache patients to determine whether prescribers follow the labeling recommendation by not prescribing this class of drugs to patients with pre-existing cardiovascular, cerebrovascular, or peripheral vascular syndromes or with cardiac risk factors.

FDA intends to solicit patients over the Internet to identify a group of triptan users. FDA will then ask these patients to complete a questionnaire about their medical history with a focus on vascular diseases. Following that, FDA will request medical records from a sample of the patients and review the submitted records to verify the medical history and the presence, if any, of cardiovascular, cerebrovascular, or peripheral vascular ischemic diseases. FDA will also collect information about patients’ demographics, route of

administration (oral, injection, intranasal), and duration of exposure to triptans.

In the **Federal Register** of November 17, 2003 (68 FR 64902), FDA published a notice requesting comment on this information collection. Three comments were received in response to the notice, each raising several issues, as follows:

(1) One comment contended that the agency has not put forth an adequate foundation for conducting the study. The comment said that no data or other information has been described to justify the expenditure of government resources and the imposition of information collection burdens on the industry. The comment said that the only rationale consists of speculation that ''it would be of great use to better understand the prescribing practices as a result of this contraindication [use of triptans in patients with vascular diseases].'' The comment contended that this is an insufficient predicate for conducting publicly-funded research that casts a cloud of suspicion over a class of currently marketed drug products that provide great clinical benefit to patients who suffer from migraine headaches. The comment said that the **Federal Register** notice provides no information about FDA's view of the relative role of data derived from the survey in relation to data from controlled clinical studies, epidemiology studies, and spontaneous medical event reports.

The comment also stated that although many marketed drugs carry contraindications and/or serious warnings, FDA has not explained how or why the triptan class of drugs was targeted for special attention. The comment said that the cumulative risk of population exposure to certain older drugs for migraine is substantially greater than the risk of exposure to the triptan class of medicines which are the newest drugs in the inventory of migraine drugs

and collectively make up only about 40 percent of the market volume for acute migraine treatments. The comment said that one consequence of the sole focus on triptan drugs could be to shift patient use to the older drugs that could be assumed to be relatively free of safety risks. The comment said that FDA implies a current problem with triptans and prejudges the outcome of the study when it says in the **Federal Register** notice ''* * *further action on the sponsor's part to improve risk management * * * [to] include further study of the problem, a labeling change, educational programs performed by the sponsor, or increased restrictions on prescribing.'' The comment said that FDA has already worked with sponsors to assure that the potential risks of use of all of these drugs are well characterized and accurately described in labeling. The comment said that to its knowledge, there are no new signals from the triptan-class of drugs.

Response: The proposed Internet-based study is a way to explore new methods to assess appropriate prescribing of drugs. Currently used methods, such as surveys of population subsets such as HMOs (Health Maintenance Organizations), are costly and difficult. The Internet may offer a convenient and efficient approach to examine prescribing practices for drugs. The proposed study is a pilot methodology study, and a first step in determining the feasibility of this approach and in determining whether FDA can detect any instances of prescribing of triptans in patients with contraindications. If Internet-based studies are in fact feasible, then FDA will design further investigations to determine their validity. The feasibility endpoints of the proposed study are demographic characteristics of respondents, case confirmation rates, and ability to document participant assertions in their medical records. Because it is a feasibility study, FDA will not make inferences

from the results regarding the appropriateness of prescribing habits. The cost of this study is relatively small. Furthermore, there is no burden to industry since members of the public and physicians' offices will be the participants.

Triptan-use is common, as is the prevalence of ischemic heart disease. A recent review of these factors in adverse event reports by FDA's Office of Drug Safety showed that the great proportion of myocardial infarctions reported in association with triptans occurred in patients who had pre-existing contraindicated conditions. These factors make this class of drugs convenient for a feasibility test of our proposed Internet-based approach.

(2) The comment also said that the proposed method of investigation is not valid and is inferior to well-accepted methodological alternatives for conducting exploratory analyses of this kind. The comment noted FDA's statement that ''* * * a signal of substantial prescribing to patients with vascular contraindications in this selected population may warrant further action on the sponsor's part to improve risk management.'' The comment contended that FDA provides neither specific details regarding how it intends to implement the study nor what it will judge to be a signal that will require action on the part of sponsors. The comment said that the absence of any definition of a signal and a sampling basis are critical flaws in the study. Another comment said FDA should deduce what proportion of patients with pre-existing cardiovascular, cerebrovascular, or peripheral vascular disease would constitute a ''signal'' in the study protocol, and specify what level of ''improvement of risk management'' (for example, further study of the problem, a labeling change, educational programs, increased restrictions on prescribing) will be required in response to the observed signal. This predetermined signal should also be the basis for the sample size calculation.

Response: This is a pilot study with an objective of evaluating the feasibility of the Internet-based approach and determining whether FDA can detect any instances of prescribing of triptans in patients with contraindications. The sample size for the study was selected based on a consideration of practicality and cost. The practical objectives of the study include, but are not limited to, determining whether enough patients can be recruited in a reasonable amount of time, whether patient questionnaires will be filled out completely, and whether FDA can document participant assertions in their medical records. FDA notes that, as with all study designs, the Internet-based approach is subject to some methodological weaknesses, but FDA intends to explore whether the use of the Internet can be an efficient means of conducting this type of study. Despite these limitations, FDA believes this approach has greater internal validity than a system of spontaneous reporting because of the inherent underreporting and potential bias involved with the latter method. If the findings of the pilot study suggest the need for further study in a larger setting, such as a managed care database, FDA anticipates that the results would be used to help plan for such future studies. FDA does not anticipate taking regulatory action based on the conclusions of the proposed study, nor will we extrapolate the frequency of apparent mis-prescribing to the general patient population. Therefore, it would be premature to define at this stage what would constitute an appropriate signal. If the survey indicates prescribing problems with triptans in migraine headache patients with vascular disease, then FDA can define what would constitute such a signal for future studies.

(3) Another comment said it is unclear how patients will be invited to take part in the survey. An open invitation would result in a significantly

biased sample, particularly if the goal of the survey is being mentioned, and this bias would not be resolved by the subsequent checking of medical records. The comment said that other sources of error inherent in the study include coverage, nonresponse, and measurement and sampling error. Measurement error is introduced due to the survey medium or due to poorly written questions/scales. Sampling error is the error associated with taking a sample of respondents and not a census, and it is impractical to conduct a random sample among online respondents. The comment said a small, voluntary survey will provide results that essentially represent testimonial evidence that can only support the hypothesis being evaluated.

Response: FDA plans to use search engine web-pages as the primary recruitment platform for all cases. Participants will only be eligible for the study if they have been prescribed triptans or ergot alkaloids, and they will not be recruited into the study based on contraindicated comorbidities. Therefore, self selection bias (in relation to ischemic heart disease) is not likely. Participants will be recruited into the study by an advertisement linked to the keywords for migraine (for example, migraine, chronic headache, and so forth) and not for vascular disorders. Therefore, anyone searching for information on migraine headache can apply to participate in the study.

FDA agrees that the study is not constructed as a population-based survey, nor could its results be used to compute rates in the general population. However, the demonstration of its feasibility, together with a description of the characteristics of participants, will provide insights into its likely utility. For example, it could form the basis for comparative studies or other innovative methodologies for determining characteristics of patients being prescribed pharmaceuticals.

There is support for the value of online random surveys. By August 2003, surveys on Internet usage by the Bureau of International Information Programs, U.S. Department of State, indicated that the U.S. online population had reached approximately 126 million (Ref. 1). These data suggest that over two-thirds of adults in the United States now regularly access the Internet. The Internet is rapidly becoming part of the population's daily activities. Information gathered by the Pew Internet & American Life Project through telephone interviews in 2004 shows that ''the vast majority of Americans say the Internet plays a role in their daily routines and that the rhythm of their everyday lives would be affected if they could no longer go online.'' Nielson NetRatings has performed monthly surveys of Internet users to compile demographic reports. Their results are based on individuals responding to solicitations and are likely to be applicable to individuals responding to advertisements to participate in Internet-based studies. In their February 2004 survey, the modal age range was 35 to 49 years, representing 33 percent of Web users. Seventeen percent were aged >55 years, representing about 21 million individuals. Overall, 47 percent of users were women, a significant rise from 1998.

Programs of Internet-based epidemiologic and clinical studies are already well underway among a number of research groups. One of the first was the Epidemiologic Cyberspace Cohort Study (Refs. 2 and 3). This study solicited participation over the Internet and used electronic registration as a surrogate for a signed consent. Data were collected by questionnaire modules and were encrypted during submission. Lenert and colleagues tested the feasibility and validity of online quality-of-life studies among individuals with ulcerative colitis (Refs. 4 and 5). The same team also explored the feasibility of

longitudinal outcomes studies of Internet users who have ulcerative colitis (Refs. 4 and 5). The Internet has also been used to administer interventions such as smoking cessation programs and the Arthritis Self-Management course (Refs. 6 and 7). It has been explored as a way to research migraine headaches (Refs. 8 and 9), and to measure self-reported disease activity in rheumatoid arthritis (Ref. 10). A methodologically successful Internet-based clinical trial of glucosamine was conducted and its results are described in publications in the *British Medical Journal* and the *American Journal of Medicine* (Refs. 11 and 12).

(4) A comment said that an Internet-based, patient directed survey would be inherently biased and would provide inaccurate information. The comment explained that spontaneously obtained adverse event data is sensitive to many external factors, and that reports solicited via an Internet survey will share some of the same shortcomings of selection/reporting bias as spontaneous reports. The comment said that because the premise for the study has now been publicly described, a balanced response is questionable and FDA will be unable to quantitatively correlate the number of cases identified with the actual rate of occurrence of inappropriate prescribing among users of triptans. The comment also contended that Internet-based studies have significant potential to attract patients that disproportionately fit the profile of interest and are not representative of the population of triptan users at large, and would provide biased information regarding the true rate or strength of the signal. The comment said it would be more productive to explore the possibility of inappropriate prescribing by using drug utilization databases and complementary epidemiological research. The comment noted that FDA acknowledged that the study population obtained through the study would

most likely not reflect the population of users of triptan drugs at large, and asked how this statement is reconciled with the goal of estimating the rate of inappropriate prescribing.

Another comment suggested an alternative strategy for the survey. The comment said that information bias or recall bias (for example, concomitant medications and medical history) can be avoided by using medical claims and pharmacy databases. By utilizing a large managed care database, the comment said it would be possible to identify triptan users through pharmacy data, and then to determine the rate of vascular disease and risk factors by reviewing the linked medical records.

Response: FDA agrees that the study population obtained through Internet-based recruitment may not reflect the general population of triptan users. Therefore, FDA is placing the following restriction on the definition of the source population: Individuals who use search engines with which the study Web site is registered. As reported in other studies, it is likely that this sample will resemble Internet users in general because the sample is drawn from among such users. Furthermore, it might allow the agency to define a source population that would represent an epidemiologically valid sampling frame for future studies. FDA does not intend to generalize to the general patient population the findings of this pilot study regarding the use of triptans in patients with contraindications. That is, FDA will not quantitatively correlate the number of cases identified with the actual rate of occurrence of inappropriate prescribing among users of triptans. Rather, this pilot study represents a first attempt to examine the feasibility of this approach and to determine whether FDA can detect any instances of prescribing of triptans in patients with contraindications. The goal of testing the Internet as a study

platform is to avoid the prohibitive burden and expense of other types of studies. If the findings of the pilot study suggest the need for further study in a larger setting, such as a managed care database, FDA anticipates that the results would be used to help plan for such future studies.

(5) Several comments said that information obtained from the proposed Internet-based study will have limited validity for a number of reasons, and that there are several potential shortcomings with an Internet-based survey that may result in selection and/or information bias and may make it difficult to draw the following valid and meaningful conclusions:

(a) The target audience will not accurately reflect the population of triptan users because comparisons of telephone/mail surveys and Internet-based surveys indicate there are significant differences in response propensity by several demographic, health, and treatment characteristics, including education, sex, age, race, socioeconomic status, computer literacy/access to the Internet, and patient satisfaction/dissatisfaction with their physician/treatment.

Response: FDA agrees that the study population obtained through Internet-based recruitment may not entirely reflect the general population of triptan users. However, this approach might allow FDA to define a source population that would represent an epidemiologically valid sampling frame for future studies. As explained above, FDA does not intend to generalize the findings of this pilot study regarding the use of triptans in patients with contraindications to the general patient population. Also, this sample will likely resemble that of Internet users in general. It is of note that Internet use in the population has risen progressively during the last few years and continues to increase (Ref. 1). Current estimates indicate that 128 million Americans use the Internet regularly. Furthermore, recent Internet-based

studies do not show major biases. For example, the Online Glucosamine Trial recruited a sample that was similar to those observed in traditional trials and included many women, elderly individuals, and individuals with low incomes (Ref. 12). An online lupus case-control study was also able to recruit a control group that resembled Internet-users as a whole, including a similar proportion of African American participants (Ref. 13). Thus, the pilot study represents a first attempt to examine the feasibility of this Internet-based approach and determine whether FDA can detect any instances of prescribing of triptans in patients with contraindications.

(b) The study will involve selection bias because the respondents will be self-selected, have little incentive to complete an Internet questionnaire, and are therefore more likely to have suffered adverse events from the use of triptans. In the absence of a true denominator, the comment said it would not be possible to calculate with accuracy the prevalence of vascular disorders which contraindicate the use of triptans. The comments stated that respondents to an Internet survey are unlikely to be representative of triptan users on the very characteristic that is being studied. Respondents may be more likely to have adverse events with triptans and medical histories that are positive for pre-existing cardiovascular, cerebrovascular, or peripheral vascular disease. Thus, the comment concluded that the prevalence of pre-existing vascular disease among triptan users may be dramatically overestimated.

Response: Participants will only be eligible for the study if they have been prescribed triptans or ergot alkaloids, and they will not be recruited into the study based on contraindicated comorbidities. Participants will be recruited into the study by an advertisement linked to the keywords for migraine (for example, migraine, chronic headache, and so forth) and not for vascular

disorders. Therefore, anyone searching for information on migraine headache can apply to participate in the study and selection bias is not likely. The information that the FDA is collecting is related to patients experiencing a contraindication before exposure to triptans and not adverse events from the use of triptans.

(c) The study may select against a large group of migraine sufferers because migraine is a disorder more common in individuals with low education and low socioeconomic status (SES), and Internet users have a higher SES. This design would permit a demonstration that some migraine sufferers receive triptans despite cardiovascular-relative contraindications, but will not permit an estimate of the prevalence or incidence of inappropriate prescribing.

Response: FDA agrees that participants might have a higher SES. However, this factor is expected to influence the generalizability of the study results but not the internal validity of the work. In addition, this factor might bias the results towards the null and would not likely flag a problem that does not exist. As mentioned earlier, FDA does not intend to generalize the study findings to all migraine patients or estimate a prevalence or incidence of inappropriate prescribing.

(d) The lack of accuracy of patient self-reporting of medical diagnoses and the timing of adverse events could also lead to significant information and recall bias. In addition, the significance of a reported adverse vascular outcome in a respondent who has used a triptan in the past may be unclear. With a lack of veracity in assuring the accuracy of the medical information reported, it will be difficult and inadvisable to draw meaningful conclusions from the study. The dynamic environment, process of informed consent, and clinical decisionmaking which takes place in the context of a private patient-physician

encounter, cannot be reliably reproduced even with accurate completion of the questionnaire and ascertainment of the medical record.

Response: Participants in the proposed study will be thoroughly authenticated through the process of obtaining informed consent, approved by both FDA and the data contractor's institutional review board, and by reviewing copies of their medical records. Consent forms will authorize the FDA investigator and data contractor to obtain further information about the patient's disorder by means of a checklist sent to their physician and copies of their medical records. The consent form will ask the patients for permission to write to their physician and/or hospital to request documentation of their migraine or other medical disorders. It will ask respondents to confirm their identity and will emphasize the legal nature of the document.

(6) Several comments suggested certain areas for inclusion in the final protocol for the proposed study and said that the proposed study must be explicit and address the following points:

(a) A strategy for identifying a representative sample of migraine sufferers treated with triptans and a method by which this population is contacted and the description of the rationale and purpose of the study used to convince patients to complete the questionnaire (the method must be free of bias and coercion); another comment asked for a description of the means by which patients will be obtained for participation (e.g., mail, e-mail, Web sites, doctor offices, pharmacies, and so forth);

Response: FDA will use search engine Web pages as the primary recruitment platform for all cases. FDA will place advertisements on the search engine sites, and will register the study site with each of the search engines,

using a set of key terms (for example, migraine, chronic headache, and so forth).

(b) The rationale and power calculations used to define the 500 participants;

Response: FDA selected the sample size based on a consideration of practicality and cost. This is a pilot study with an objective of evaluating the feasibility of the Internet-based approach and determining whether FDA can detect any instances of prescribing of triptans in patients with contraindications. Practical objectives include, but are not limited to, determining whether enough patients can be recruited in a reasonable amount of time, whether patient questionnaires will be filled out completely, and whether FDA can document participant assertions in their medical records. If the findings of the pilot study suggest the need for further study in a larger setting, such as a managed care database, FDA anticipates that the results will be used to help plan for such future studies. FDA will not extrapolate the frequency of apparent misprescribing to the general patient population.

(c) Any proposed incentive for patients to participate in the study.

Response: There are no incentives offered for patients to participate in the pilot study.

(7) Another comment raised the following additional issues about the proposed Internet-based survey:

(a) There is no specific question about whether a patient has ever been prescribed a triptan for treatment of his/her migraine headaches;

Response: The question about migraine medications states: ‘‘Please check the box for each medication that has ever been prescribed to you for migraine

treatment.'' Therefore, the information suggested by the comment will be captured.

(b) Because some triptans have a variety of formulations and others do not, only the appropriate route(s) of administration for each triptan should be listed in the questionnaire to avoid invalid data;

Response: Information on the exact formulation of triptans will be collected.

(c) The questions regarding triptan prescribing and medical history are not constructed in a way that the compliance of prescribers can be evaluated appropriately, resulting in a false-positive response;

Response: The questions about triptan prescribing request information about the dates of the prescription and how often it is used. In addition, the medical history questions also ask about the timing of the medical conditions. Therefore, such information will be sufficient to assess compliance of prescribers and concurrent use of other medications.

(d) It is not clear whether FDA will use the data collected in the ''Medications'' section to evaluate concurrent or contemporaneous medication use among triptan users—this information would not be sufficient to assess whether other medications are taken concurrently or contemporaneously with triptans.

Response: Data will be collected on other medications taken by patients. However, evaluating concurrent medication use among triptan users is not one of the primary goals of the study.

(e) Because of the unrestricted access to the survey, there is the potential for fraudulent entry of information.

Response: As mentioned earlier, participants in the proposed study will be thoroughly authenticated through the process of obtaining informed consent and reviewing copies of their medical records.

(f) Relevant and complete medical records of all respondents must be reviewed. In addition, the method by which additional medical information will be acquired for incomplete cases must be addressed, or the criteria for discarding a case when the necessary medical data is incomplete must be explicit.

Response: As mentioned earlier, the consent forms that patients will sign will authorize the FDA investigator and data contractor to obtain further information about the patient's disorder by means of a checklist sent to their physician and copies of their medical records. If these records do not verify what the patient reported, the case will be discarded.

(8) Two of the comments discussed the Health Insurance Portability and Accountability Act (HIPPA) and its regulations and how it may affect the proposed study.

The comments requested that the study protocol address how the completion of an Internet-based questionnaire and the review and sampling of patient records would comply with the HIPPA regulations regarding medical privacy. A comment said that the method by which medical records and questionnaires will be de-identified may conflict with HIPPA regulations. The comment also asked for a description of the method and the appropriateness of obtaining a waiver from the new HIPPA regulations. Another comment said that the proposed study needs to address the method of review of medical records: For example, the proportion of patients' medical records that will be reviewed, the means to obtain informed consent, strategies to be used to

address constraints on record access due to HIPAA regulations, responsibility for medical chart review, medical record abstracting forms, and other ways of verifying medical history when medical records are not available or incomplete. Another comment said that the accuracy of self-reported vascular disease on the Internet is uncertain and that this limitation might be partially offset by a medical record review in a subset of respondents to confirm the accuracy of self-reporting. However, the comment said, a representative sampling of patient records may be restricted by the HIPAA regulations.

Response: The proposed study, including the Internet-based questionnaire and review and sampling of patient records, does not violate the HIPAA regulations, 45 CFR parts 160 and 164. The signed consent form, in accordance with the HIPAA regulations, authorizes the physician and/or hospital to provide documentation of the patient's migraine or other medical disorders. The signed consent form also authorizes, in accordance with the HIPAA regulations, the study investigators to receive and use this medical record information.

All information that allows direct identification of participants will be omitted from the study databases. These databases will only contain information of a nonsensitive nature. Safeguards will be imposed to prevent tampering or accessing of these data by nonstudy personnel. All hardcopy information, including copies of medical charts, will be stored in a locked filing cabinet in a locked office at the FDA data contractor's site. The data will be used for study purposes only and will not be distributed to other parties without the participant's permission. The identities of all individuals who participate as ''cases'' of triptan users with vascular disease and at least 20 percent of the remainder of patients will be thoroughly authenticated through

the process of obtaining informed consent and reviewing copies of their medical records. Consent forms will authorize the investigator to obtain further information about their disorder by means of a checklist sent to their physician and copies of their medical records. The consent form will ask them for permission to write to their physician and/or hospital to request documentation of their migraine or other medical disorders. It will ask respondents to confirm their identity and will emphasize the legal nature of the document.

(9) A comment said that before conducting the study, FDA should consult with sponsors of marketed triptan drugs and other companies with research, development, and commercial marketing experience about optimal study design and assessment. The comment also said that prior to implementing the study, FDA should disclose specific details about the proposed collection (for example, how the purpose of the survey will be explained to patients, a prospective definition of a ''signal,'' and so forth), and offer an opportunity for public comment on these specifics. Another comment described the findings of a panel it convened to evaluate the scientific and clinical data on triptan-associated cardiovascular risk and to formulate consensus recommendations to guide health care providers in making informed prescribing decisions for patients with migraine. The comment also described other studies containing estimates of the rates of various vascular diseases and cardiac risk factors among patients using triptans. The comment contrasted these studies with the proposed FDA Internet-based study and said that the FDA proposed study has a number of methodological limitations that may produce misleading data and may lead to a renewed and unnecessary sense of alarm among patients and practitioners.

Response: The purpose of the November 17, 2003, **Federal Register** notice was to describe the proposed study and offer an opportunity for comment by the sponsors of marketed triptans. The responses to the comments in this notice also provide additional explanation and another opportunity for all interested parties to participate through additional comments. In addition, FDA has responded in this document to those comments expressing concern with the study methods.

References

The following references have been placed on display in the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site address, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. Who Online: Pew Internet & American Life Project, February–March 2005 Tracking Survey, 2005.

2. Dorgan, J.F., M.E. Reichman, J.T. Judd, C. Brown, C. Longcope, A. Schatzkin, et al., ''The relation of reported alcohol ingestion to plasma levels of estrogens and androgens in premenopausal women (Maryland, United States),'' *Cancer Causes Control,* 5(1):53–60, 1994.

3. Kushi, L.H., J. Finnegan, B. Martinson, J. Rightmyer, C. Vachon, L. Yochum, ''Epidemiology and the Internet,'' [letter; comment], *Epidemiology* 1997;8 (6):689–90, 1997.

4. Soetikno, R.M., R. Mrad, V. Pao, L.A. Lenert, ''Quality-of-life research on the Internet: feasibility and potential biases in patients with ulcerative colitis,'' *Journal of the American Medical Informatics Association,* 4(6):426–35, 1997.

5. Soetikno, R.M., D. Provenzale, L.A. Lenert, ‘‘Studying ulcerative colitis over the World Wide Web, [see comments], *American Journal of Gastroenterology*, 92(3):457–60, 1997.

6. L. Lenert, R.F. Munoz, J. Stoddard, K. Delucchi, A. Bansod, S. Skoczen, et al., ‘‘Design and pilot evaluation of an internet smoking cessation program,’’ *Journal of the American Medical Informatics Association*, 10(1):16–20, 2003.

7. Lorig, K.R., D.D. Laurent, R.A. Deyo, M.E. Marnell, M.A. Minor, P.L. Ritter, ‘‘Can a Back Pain E-mail Discussion Group improve health status and lower health care costs?: A randomized study,’’ *Archives of Internal Medicine*, 162(7):792–6, 2002.

8. Lenert, L.A., ‘‘Use of willingness to pay to study values for pharmacotherapies for migraine headache, *Medical Care*, 41(2):299–308, 2003.

9. Lenert, L.A., T. Looman, T. Agoncillo, M. Nguyen, A. Sturley, C.M. Jackson, ‘‘Potential validity of conducting research on headache in internet populations,’’ *Headache*, 42(3):200–3, 2002.

10. Athale, N., A. Sturley, S. Skoczen, A. Kavanaugh, L. Lenert, ‘‘A web-compatible instrument for measuring self-reported disease activity in arthritis,’’ *Journal of Rheumatology*, 31:223/8, 2004.

11. McAlindon, T., M. Formica, M. LaValley, M. Lehmer, K. Kabbara, ‘‘Effectiveness of glucosamine for symptoms of knee osteoarthritis: results from an internet-based randomized double-blind controlled trial,’’ *American Journal of Medicine*, 117(9):643–9, 2004.

12. McAlindon, T., M. Formica, K. Kabbara, M. LaValley, M. Lehmer, ‘‘Conducting clinical trials over the internet: feasibility study,’’ *The British Medical Journal*, 327(7413):484–7, 2003.

13. McAlindon, T.E., M.K. Formica, C.E. Chaisson, R. Woods, J. Fletcher, ‘‘Feasibility Of An Internet-Based Case-Control Study Of Recent-Onset SLE,’’ *Arthritis Rheum*, 50(9 (Suppl)):682, 2004.

FDA estimates that approximately 500 persons will voluntarily complete the questionnaire. The estimated time for completing each questionnaire is approximately 2 hours, resulting in a total burden of 1,000 hours per year. The burden of this collection of information is estimated as follows:

TABLE 1.—ESTIMATED ONE-TIME REPORTING BURDEN[1]

No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
500	1	500	2	1,000

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

Dated: October 26, 2005.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 05–????? Filed ??–??–05; 8:45 am]

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